Gut feelings: visceral hypersensitivity and functional gastrointestinal disorders
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CHAPTER 1
DRUGS INTERFERING WITH VISCERAL SENSITIVITY FOR THE TREATMENT OF FUNCTIONAL GASTROINTESTINAL DISORDERS: THE CLINICAL EVIDENCE (Review)

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ABSTRACT

At present, the concept of visceral hypersensitivity provides the leading hypothesis regarding the generation of symptoms in functional gastrointestinal disorders (FIGDs). The most frequent of these disorders are the Irritable Bowel Syndrome (IBS) and Functional Dyspepsia (FD). This paper discusses the current clinical evidence for drugs that have been proposed to interfere with visceral sensitivity in FIGDs. Several possible pharmacological targets have been identified to reduce visceral pain and to reverse the processes underlying the persistence of visceral hypersensitivity. However, most of the available evidence comes from experimental animal models and cannot simply be extrapolated to patients with FIGDs. In this review, we selected five drug classes that have been shown to exhibit visceral analgesic properties in experimental studies, and of which data were available regarding their clinical efficacy. These included opioid substances, serotonergic agents, antidepressants, somatostatin analogues and \( \alpha_2 \)-adrenergic agonists. Although clinical trials indeed show a limited benefit, in particular for serotonergic agents, the evidence illustrating that these effects result from normalisation of visceral sensation is currently lacking. Therefore, we conclude that the concept of targeting visceral hypersensitivity as a treatment for FIGDs is still controversial. Future evaluations require patient selection based on the presence of visceral hypersensitivity and application of compounds that exhibit 'true' viscerosensory effects.

ABBREVIATIONS: FGID: Functional gastrointestinal disorder; IBS: Irritable bowel syndrome; FD: Functional dyspepsia; EC: enterochromaffin; IPAN: intrinsic primary afferent neurone; CNS: central nervous system; DRG: dorsal root ganglia; ACC: anterior cingulate cortex; NMDA: N-methyl-D-aspartate; PET: positron emission tomography; fMRI: functional magnetic resonance imaging; CI: confidence interval; SSRI: selective serotonin reuptake inhibitor; FDA: Food and Drug Administration; TCA: tricyclic antidepressant; SST: somatostatin
INTRODUCTION

Functional gastrointestinal disorders (FIGDs) are characterised by chronic abdominal pain or discomfort often associated with abnormal motility, in the absence of any detectable organic disease.\(^1\) The most frequent of these disorders are the Irritable Bowel Syndrome (IBS) and Functional Dyspepsia (FD). Although the pathogenesis of FIGDs is multifactorial, the most widely accepted mechanism responsible for the development of symptoms is increased visceral sensitivity.\(^2\) Increased gut sensitivity may lead to alterations in gut motility by altering regulatory reflex pathways and secretory functions, which in turn may lead to functional disturbances. In addition, normal, physiologic stimuli may be perceived with increased intensity (a phenomenon referred to as hypersensitivity) or may even cause pain (allodynia), whereas the perception of painful stimuli may be increased (hyperalgesia). Within the international literature, the term visceral hypersensitivity is usually applied to indicate the presence of increased sensory responses in FIGDs.

The evidence that patients with FIGDs have abnormal visceral sensitivity is illustrated by studies evaluating the sensory responses to mechanical distension of the gut. In general, patients with FIGDs report pain at distension levels that are normally not perceived as painful and the magnitude of the sensory responses to gut distension is increased. These sensory abnormalities may be organ specific, since patients with IBS exhibit hypersensitivity to distension of the colon and rectosigmoid,\(^4\) whereas patients with FD exhibit hypersensitivity to gastric distension.\(^6\) On the other hand, generalised hypersensitivity involving the total length of the GI tract has been described in both conditions.\(^8\) In addition to mechanical distension, patients with FD experience increased sensitivity to intraduodenal administration of nutrients and acid,\(^10\) whereas patients with IBS show exaggerated motor responses on food intake.\(^12\) Furthermore, patients often report tenderness of the colon (IBS) or epigastric tenderness (FD) during abdominal palpation, whereas endoscopic examinations often cause excessive pain.\(^2\) Patients with FIGDs show normal or even decreased somatic sensory responses, indicating that the sensory changes represent a distinct functional defect limited to the viscera, rather than a more general change in perception due to some type of response bias.\(^13\)

Taken together, these findings indicate that patients with FIGDs exhibit increased sensory responses to stimuli arising from the gut, which may represent a major pathophysiological mechanism underlying the generation of symptoms in these patients. However, it should be emphasised that visceral hypersensitivity is not a consistent finding in all patients with FIGDs. In IBS, hypersensitivity to colorectal distension has been demonstrated in 20-80% of patients across studies,\(^15\) and similar prevalences have been reported for FD (37-60%).\(^6\) Therefore, visceral hypersensitivity may only play a role in a (substantial) subgroup of patients with FIGDs. Although controversial, this subgroup may have a different pathogenesis compared with FIGD patients with normal gut sensitivity, and may therefore benefit from different treatments.\(^2\) In particular, FIGD patients characterised by visceral hypersensitivity may benefit from drugs that reduce visceral sensitivity or visceral analgesics. In this perspective, much progress has been made over the last
decade to characterise the mechanisms and mediators modulating visceral (hyper-)
sensitivity, mainly based on experimental data from animal models. The recent
advances in our understanding of the physiology of visceral sensation, including its
mediators and pharmacology have been reviewed extensively. However, as
stated previously, the ultimate proof of the concept that restoring normal gut
sensitivity would result in clinical benefit lies in the improvement of symptoms by
drugs that selectively reduce visceral sensitivity.

This paper discusses the currently available studies evaluating the effect of drugs
that have been proposed to interfere with visceral sensitivity in FIGDs. We selected
only those drug classes 1) with visceral analgesic properties, as shown in basic
experimental studies; 2) of which data were available on visceral sensitivity in
humans (including studies on the normal physiology of visceral sensation carried
out in healthy volunteers, as well as studies in patients with FIGDs); and 3) of
which controlled data were available addressing their clinical efficacy. In addition,
we focused primarily on those drug classes that have been proposed to have a direct
effect on visceral sensitivity. Thus, agents that may reduce visceral perception
indirectly, for example by relaxing the organ wall such as smooth muscle relaxants,
were not included.

MECHANISMS OF VISCERAL HYPERSENSITIVITY

The pathophysiological mechanisms leading to visceral hypersensitivity in FIGD
patients are unknown and most likely involve multiple levels of the viscerosensory
system. In the light of the scope of this review, we briefly summarised these
processes. For more detailed insights in neuroanatomic pathways and mediators
involved in the physiology of visceral pain and the mechanisms underlying the
development of visceral hypersensitivity, the reader is referred to the excellent
papers cited in the text and detailed references therein.

Briefly, afferent projections of gut stimuli to the central nervous system (CNS)
involves at least two 'relay stations' (Figure 1). Visceral primary afferent neurones
have their cell bodies in the dorsal root ganglia (DRG) and terminate in the dorsal
horn of the spinal cord. The second order neurones projecting from the dorsal
horn to the higher CNS centres ascend through the spinothalamic and
spinoreticular tracts and the dorsal column of the spinal cord (Figure 1). Nerve
fibres within the spinothalamic and spinoreticular tracts synapse with autonomic
centres and third order neurones in the reticular activating system, leading to
activation of thalamic centres (cognition) and limbic centres (emotion, arousal).
These centres then finally project to the prefrontal cortex, giving rise to conscious
perception (Figure 1).
The responsiveness of the viscerosensory system to gut stimuli can be modulated at several levels. Therefore, developing visceral hypersensitivity may involve peripheral, spinal and/or central regulatory mechanisms and several mediators. For example, gut inflammation can increase the gain of primary visceral afferents ('peripheral sensitisation'). In addition, continuous afferent input on dorsal horn neurones can lead to a persisting state of hyperexcitability, a mechanism referred to as 'central sensitisation'. Central sensitisation causes amplification of all afferent input projecting onto the dorsal horn neurones and increases their receptive field. This results in the phenomenon that physiological stimuli that are normally not perceived can cause pain, whereas the patterns of viscero-somatic referral may be altered.

On the other hand, dorsal horn neurones receive descending, modulatory inputs from the brain, which may be either excitatory or inhibitory. Disturbances of this modulatory system can alter spinal afferent signal transduction, and thus the intensity of stimuli that reach the higher CNS centres. This could involve regulation via autonomic (vagal) and limbic centres, partly explaining the influence of stress and emotional factors on visceral sensitivity. The brain also plays an important role in the integrative processing and the emotional ‘colouring’ of stimuli.

**Figure 1.** Pathways involved in pain control (See text). CNS, central nervous system; DRG, dorsal root ganglia. Reprinted from with permission (BMJ publishing group).
arising from the gut. Visceral stimuli can induce long-term alterations in the CNS, which may for example lead to differential activation of certain regions within the brain. This may include limbic system structures that are involved in determining the emotional-affective aspects of pain and pain suffering, such as the anterior cingulate cortex (ACC).

In contrast to the earlier belief that the vagus nerve mainly if not solely mediates functional reflexes in response to low threshold physiological gut stimuli that are normally not perceived, evidence is accumulating that this sensory nerve also plays a direct role in the perception of distinct visceral sensations. These include fullness, nausea, emesis and, under pathological conditions, even pain.

METHODOLOGY

The most widely used method of studying gut sensitivity in humans involves the assessment of perceptual responses to mechanical distension of the gut. Using this method, the concept of visceral hypersensitivity in FIGDs was first described and subsequently confirmed by others. The gold standard to date is the barostat. This method involves placement of a balloon or, preferably, a noncompliant polyethylene bag, into the organ of interest (e.g. stomach, colon, rectum). The bag is then connected to a computerised pump, which allows isobaric or isovolumetric inflation of the bag. The intensity of sensations at each distension level can be scored on a standardised intensity rating scale. Alternatively, the stimulus intensity at which a certain predefined sensation (e.g. urge to defecate, pain) is perceived (i.e. the perceptual threshold) can be determined. Technical recommendations of improving the reproducibility of gut distension tests, including their limitations and pitfalls, have been discussed by others.

In addition to mechanical distension, sensations can be induced by electrical stimulation of the gut, using an intraluminal electrode with increasing stimulus intensity. Other methods of assessing gut sensitivity involve intraluminal application of chemical stimuli, such as nutrients and acid. Notably, combined stimuli may further enhance viscerosensory responses. For example, intraduodenal infusion of lipids increases the sensitivity to gastric and colonic distension. The sensitivity to gastric distension also increases during intraduodenal infusion of acid. Similarly, Intragastric acid infusion sensitises the oesophagus to distension and electrical stimulation, and has been proposed as a model for the study of visceral hypersensitivity in healthy volunteers.

Although there are several ways of limiting response bias, methods that assess perceptual responses inevitably hold an element of subjectivity. Therefore, alternative techniques have been introduced to assess visceral sensory responses in a more objective manner. To evaluate viscerosensory processing at the level of the CNS, different electrophysiological techniques have been used. These include recording of cerebral and spinal evoked potentials in response to visceral

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stimulation (a technique based on the principles of the electroencephalogram)\textsuperscript{35}, and reflexologic techniques.\textsuperscript{36}

Methods of studying the processing of gut stimuli at the level of the brain further include functional brain imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).\textsuperscript{37} PET and fMRI are techniques that demonstrate changes in regional cerebral blood, as a measure of brain activation. Currently, their application for clinical evaluations is limited, mostly because of technical limitations such as a low spatial resolution and signal to noise ratio.\textsuperscript{15,37} However, assessing sensory responses at the level of the brain could be crucial to further expand our understanding of FIGDs.

**DRUGS MODULATING GUT SENSITIVITY IN HUMANS**

Several mediators have been proposed as possible pharmacological targets for reducing visceral sensitivity and perception.\textsuperscript{2,3,16,17,21,23,26} The majority of the compounds aimed at these targets have only been studied in experimental animal models. These studies have certainly contributed to our understanding of the (patho-) physiology of visceral sensation and visceral pain. In this review, we only selected drugs with proposed visceral analgesic properties that have reached the stage of evaluation in humans, including efficacy studies in FIGDs. The five drug classes that met these criteria were opioid substances, serotonergic agents, antidepressants, somatostatin analogues and $\alpha_2$-adrenergic agonists. Other compounds that have been evaluated for their proposed viscero-sensory effects in humans, but not for their clinical efficacy, include NMDA receptor antagonists, prostaglandin receptor antagonists, calcium channel blockers, and nitric oxide synthase inhibitors.\textsuperscript{31,38-40} In particular, NMDA receptors may represent an interesting target to modulate visceral hypersensitivity. Although NMDA receptor antagonists failed to reduce normal visceral perception,\textsuperscript{38} studies with ketamine in the model of acid-induced oesophageal hypersensitivity in healthy volunteers, have suggested that NMDA receptors play a role in the development of central sensitisation.\textsuperscript{41} Using the same model, comparable effects were seen after treatment with the prostaglandin E2 receptor-1 antagonist ZD6416.\textsuperscript{31} Similar studies in FIGD patients may further expand our understanding of the concept of visceral hypersensitivity. Calcium channel blockers may also specifically interfere with hypersensitive conditions. For example, nicardipine increased perceptual thresholds in patients with IBS, but not in healthy volunteers.\textsuperscript{39} Nitric oxide synthase inhibitors have not been shown to have any viscero-sensory effects in healthy subjects under normal, physiological conditions.\textsuperscript{40,42} However, the possible role of nitric oxide in mediating nociceptive processing in experimental models of hypersensitivity may warrant further evaluation in humans.\textsuperscript{43}

We carefully selected those drug classes that had an a priori potential of reducing visceral sensitivity, based on experimental animal data. One of the difficulties in the interpretation of the true viscero-sensory effects of a particular
drug during mechanical distension of the gut involves its relative action on the viscoelastic properties of the gut wall. Changes in compliance or tone of the gut wall may alter volume thresholds, without associated effects on pressure based distensions. Although we did not include agents that may reduce visceral perception indirectly, such as smooth muscle relaxants, some of the selected compounds appeared to have significant gut wall relaxing properties. Therefore, these compounds cannot be considered as ‘pure’ viscerosensory drugs, as will be discussed below.

OPIOID SUBSTANCES

General
The antinociceptive properties of opioid agonists have been widely established. Opioid agonists inhibit the perception of somatic and visceral pain through their action on opioid receptors, involving the μ-, δ- and κ-opioid receptor subtypes. The antinociceptive effects of selective ligands acting on μ- and δ-receptors involve hyperpolarisation of neurones, whereas κ-agonists have been shown to modulate intracellular ion conductance. Variable numbers of the different opioid receptors have been demonstrated not only in the brain and the spinal cord, but also in the periphery, including in the dorsal root ganglia (DRG), on primary afferent neurones and their sensory nerve endings.

In somatic pain, selective μ-, δ- and κ-opioid receptor agonists have been shown to block nociceptive responses in experimental animal models, and have been successfully applied for clinical use. Similarly, there is evidence that pain arising from the viscera is reduced by opioid receptor activation. For example, the cardiovascular reflex response to noxious balloon distension of the duodenum in the rat was inhibited by the μ-opioid agonist morphine, but also by the κ-opioid agonists fedotozine and U-50488. Similarly, morphine, fedotozine and U-50488 reduce nociceptive reflexes upon noxious distensions of the colon, both in anaesthetised and awake rats. In addition to acute visceral pain, both μ and κ opioid agonists have been shown to be effective in attenuating nociception in experimental models of visceral hypersensitivity. For example, morphine, fedotozine and U-50488 attenuated the hypersensitive response to colonic distension following a chemically induced colitis in the rat.

With regard to their application in FIGDs, both μ- and κ-opioid agonists have direct peripheral antinociceptive effects, but may also induce significant centrally mediated side effects. However, fedotozine does not cross the blood brain barrier after peripheral administration. These combined properties of fedotozine could theoretically lead to antinociceptive effects without the central side effects and the addictive potential of other opioid compounds.

μ-Opioid agonists
Viscerosensory effects in humans: The effects of the μ-opioid agonist fentanyl on the perceptual responses to phasic, isobaric rectal distension was studied in both
healthy volunteers and patients with IBS. Intravenous fentanyl significantly and dose-dependently increased the thresholds for discomfort and pain in both healthy controls and patients. In addition, fentanyl decreased the ratings of intensity and unpleasantness of the stimulus. Because rectal tone and rectal wall compliance were not altered, it was concluded that fentanyl directly affects afferent signalling. Similar results were obtained in a study on postoperative pain, in which patients undergoing a hysterectomy were randomised to receive morphine or tramadol, a classical \( \mu \)-opioid agonist and an atypical opioid analgesic, respectively. Although not very physiological, this study showed that morphine infusion increased pain thresholds during rectal distension, whereas tramadol infusion showed a similar but non-significant trend.

Despite their viscerosensory effects, the clinical application of \( \mu \)-opioid agonists for FIGDs is limited because of their well known prominent centrally mediated side effects and addictive potential.

**\( \kappa \)-Opioid agonists**

*Viscerosensory effects in humans:* The possible visceral antinociceptive effects of the \( \kappa \)-opioid agonist fedotozine have been studied in healthy volunteers and in IBS patients only. In healthy volunteers, pre-treatment with fedotozine (30 mg three times daily) significantly increased the threshold for discomfort during stepwise, isobaric gastric distension. In addition, fedotozine reduced the inhibition of the R\( \text{III} \) reflex induced by gastric distension. This technique involves electrical stimulation of a (somatic) cutaneous sensory nerve, eliciting a polysynaptic reflex that can be recorded from a flexor muscle on the ipsilateral limb (i.e. the R\( \text{III} \) reflex). Gut distensions have been shown to inhibit the R\( \text{III} \) reflex, which has been proposed to be related to activation of spinal and/or supraspinal modulatory systems. Reduction of this inhibitory action may thus suggest a specific inhibitory action on spinal visceral afferent pathways. Gastric wall compliance was not altered by fedotozine.

In IBS, intravenous infusion of fedotozine (100 mg) significantly increased thresholds for first perception and pain during isobaric, phasic distension of the colon (Figure 2). This effect was observed without changes in colonic tone or colonic wall compliance. Compared with healthy controls in other studies, fedotozine normalised the sensory thresholds to colonic distension, and thereby colonic mechanosensitivity. Data on visceral perception in FD patients are currently lacking.

*Clinical efficacy:* Despite its effect on visceral sensitivity in IBS patients and healthy volunteers, fedotozine was found to produce disappointing clinical benefits for the treatment of FIGDs. In a double blind, placebo controlled, dose response trial involving 238 patients with IBS, fedotozine at the highest dose (30 mg three times daily) improved symptoms of pain and bloating significantly better than placebo. However, in terms of clinical significance, the results were less impressive. For example, the primary efficacy endpoint, i.e. the weekly trend of
maximal daily pain scores (0 = absent; 4 = very severe), decreased from 1.8 at inclusion to 1.3 after six weeks treatment with fedotozine, whereas during placebo these scores decreased from 1.7 to 1.5 (Figure 3). Furthermore, secondary efficacy measures evaluating bowel functions showed no significant improvement.

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**Figure 2.** Effect of fedotozine on colonic sensitivity in IBS patients: Cumulative number of patients positively responding for the pain threshold on placebo and 100 mg fedotozine intravenously. Adapted from with permission (Elsevier Health Sciences).

**Figure 3.** Clinical efficacy of fedotozine in IBS patients: Changes (%) in the weekly mean of maximal daily pain reported by patients per group A) expressed as the percentage of the baseline score at the end of the two-week placebo washout period; and B) expressed as the numerical score per week on a 0-4 scale (mean ± SD). By the end of the study, the changes from baseline were significantly greater than placebo during the highest dose. However, numerical pain scores were similar. Adapted from with permission (Kluwer Academic/Plenum Publishers).
Similarly, in patients with FD, two large trials showed statistically significant improvement over placebo for overall symptom intensity and individual dyspeptic symptoms, but again, the true therapeutic gain was limited. The first study was a double blind, placebo controlled dose ranging study (10, 30 and 70 mg three times daily for six weeks) in 146 patients with FD. A statistical analysis indicated that the two higher doses of fedotozine were significantly more effective in reducing the mean symptom scores for postprandial fullness, bloating, abdominal pain and nausea. However, the maximal reduction in symptom scores compared to baseline (7-point scale ranging from 0 to 6) was approximately 1.1 points with placebo and 1.8 points with fedotozine.

The second study on fedotozine for FD (in a dose of 30 mg three times daily) was a multi-centre, placebo controlled phase III efficacy study, involving 271 patients. The primary efficacy endpoint was the patient's self-assessment of overall symptom intensity (five-point scale ranging from 0 to 4). After six weeks treatment the improvement of the overall symptom intensity score was significantly greater in the fedotozine group compared to placebo recipients (treatment effect 18%). However, in absolute terms, the overall symptom intensity score decreased from 1.6 at baseline to 1.1 in patients on fedotozine, while patients on placebo improved from 1.5 to 1.2. The degrees of improvement for individual dyspeptic symptoms (pain, nausea) were of the same magnitude.

At present, fedotozine is no longer under evaluation, although other selective κ-opioid agonists are still under consideration.

Other opiate compounds

**Trimebutine:** Other, less specific opiate compounds with demonstrated efficacy in the treatment of IBS are trimebutine and loperamide. A recent meta-analysis of four placebo controlled trials showed significant benefit for trimebutine over placebo for global assessment (odds ratio 3.45; 95% CI: 2.03-5.86). However, although trimebutine acts as a weak agonist of peripheral μ-, κ- and δ-opioid receptors, it has been considered primarily to be a smooth muscle relaxant. In addition, there are no data available confirming its potential modulatory action on visceral sensitivity in humans. Therefore, the mechanism(s) by which trimebutine may be beneficial in IBS remain incompletely understood.

**Loperamide:** Several placebo controlled trials have demonstrated the efficacy of loperamide in IBS, not only by improving diarrhoea (stool frequency and stool consistency) but also by a reduction in pain intensity and urgency. It should be emphasised however that these studies were relatively limited in size. Interestingly, loperamide has been shown to produce potent antinociception in a variety of inflammatory models of somatic hyperalgesia in rodents. Since the compound does not cross the blood brain barrier in significant amounts, loperamide probably induces antinociception via activation of peripheral opioid receptors. Whether this is also true for visceral pain is not known. However, the clinically observed effects on pain intensity and urgency could suggest that the beneficial effects of loperamide in IBS might not only reflect its antidiarrhoeal properties, but rather a combined...
action on propulsion and afferent signalling.\textsuperscript{61-63} Based on the available evidence, these issues remain speculative.

**Opioids: Summary**

There is convincing evidence that both \( \mu \)- and \( \kappa \)-opioid receptor agonists reduce gut sensitivity in humans, both in normal control subjects and in patients with IBS. The application of \( \mu \)-opioid agonists for clinical practice is limited because of their centrally mediated side effects and addictive potential. In contrast, fedotozine acts on peripheral \( \kappa \)-opioid receptors, producing antinociception without affecting CNS functions. Therefore, fedotozine was initially introduced with high expectations for its possible benefit in the treatment of FIGDs. However, the clinical benefits of fedotozine for both IBS and FD have been disappointing. On the other hand, less specific opiate compounds such as loperamide and trimetrexate have been shown to provide significant clinical benefit for IBS with excellent tolerability. Although these compounds have other properties that may explain their beneficial effects on IBS symptoms, such as slowing gut transit and relaxing the gut wall, their possible viscerosensory effects in humans have not been explored.

**SEROTONERGIC AGENTS**

**General**

There are seven known serotonergic (5-HT) receptors, of which 5-HT\(_1\), 5-HT\(_3\) and 5-HT\(_4\) receptors (and their subtypes) seem to play the most important role in the gut.\textsuperscript{66} 5-HT is released by mucosal enteroendocrine cells in response to intraluminal stimuli and diffuses across the basal membrane. Via activation of 5-HT\(_{1B/D}\) / 5-HT\(_4\) receptors on the nerve endings of intrinsic primary afferent neurones (IPANs), 5-HT plays a key role in stimulating peristalsis and secretion.\textsuperscript{66,67} Excitatory 5-HT\(_3\) receptors have been identified on IPANs, afferent sensory fibres and DRG neurones. Blocking these receptors reduced visceral pain in rats.\textsuperscript{68,69} Similarly, the 5-HT\(_4\) partial receptor agonists tegaserod reduced visceral afferent firing during colorectal distension in cats,\textsuperscript{70} whereas 5-HT\(_{1A}\) and 5-HT\(_{1B}\) receptor agonists have been shown to decrease the visceromotor response to noxious colorectal distension in rats.\textsuperscript{71} Thus, application of both 5-HT agonists and antagonists, acting on different 5-HT receptors, may hold promise for the treatment of visceral pain.

Because disturbances of one or more of these factors may contribute to the functional abnormalities found in FIGDs, several compounds targeting these receptors have been developed for their possible use in the treatment of FIGDs.\textsuperscript{66,72} These compounds include the 5-HT\(_3\) receptor agonists alosetron, ondansetron, granisetron, tropisetron and cilansetron, and the 5-HT\(_4\) receptor agonists cisapride, prucalopride and tegaserod. In addition, other available serotonergic compounds have been evaluated for their possible effects on gastrointestinal function, such as the anti-migraine drug sumatriptan and the anxiolytic drug buspirone, both agonists
of specific 5-HT\textsubscript{1} receptor subtypes. The possible effects of selective serotonin reuptake inhibitors (SSRIs) on gut sensitivity are discussed separately.

5-HT\textsubscript{1} agonists  

*Viscerosensory effects in humans:* Sumatriptan and buspirone, acting at different subclasses of 5-HT\textsubscript{1} receptors (5-HT\textsubscript{1B/1F} and 5-HT\textsubscript{1A}, respectively) have been shown to increase intragastric volumes needed to induce perception and discomfort in healthy volunteers.\textsuperscript{73,74} However, this was associated with a marked reduction in gastric tone. Similarly, in FD patients, sumatriptan and buspirone decreased sensitivity to gastric distension by enhancing gastric relaxation.\textsuperscript{75,76} In the colon, buspirone did not significantly alter compliance, tone, or sensation relative to placebo.\textsuperscript{77} These data indicate that 5-HT\textsubscript{1} agonists may only alter viscerosensory responses to gut distension via smooth muscle relaxation, but not via a direct effect on visceral sensitivity.

*Clinical efficacy:* Although randomised controlled clinical trials are not available, there is some evidence that 5-HT\textsubscript{1} agonists may reduce postprandial symptoms in patients with FD. For example by enhancing gastric accommodation, sumatriptan increased the maximum ingested volume of a liquid test meal at which patients with FD reported satiety.\textsuperscript{78} However, these effects could not be confirmed by others.\textsuperscript{79} Furthermore, in a preliminary placebo controlled, crossover trial in 18 FD patients, buspirone significantly decreased the meal related symptom scores, which was associated with enhanced gastric relaxation and decreased gastric emptying.\textsuperscript{76} It should be emphasised that the potential benefits of buspirone in FIGD patients may also largely depend on its broad psychotropi c properties,\textsuperscript{80} since the incidence of concomitant psychiatric disorders, in particular depression and anxiety, is high in these patients.\textsuperscript{81}

5-HT\textsubscript{3} antagonists  

*Viscerosensory effects in humans:* The viscerosensory effects of different 5-HT\textsubscript{3} receptor antagonists in humans have been extensively evaluated. Most of the available studies evaluated the effects of ondansetron\textsuperscript{82-84} and alosetron\textsuperscript{85-87} whereas two additional studies used tropisetron and granisetron, respectively.\textsuperscript{88,89} In summary, none of the agents studied had significant effects on the perceptual responses to pressure based distensions of the proximal stomach\textsuperscript{82,85,88} or colorectum.\textsuperscript{82,84,86,87} This lack of viscerosensory effect was observed in both FIGD patients (mainly IBS)\textsuperscript{82,86-89} and healthy volunteers.\textsuperscript{82,85,88} In contrast, both alosetron and granisetron increased the volume thresholds inducing discomfort during colorectal distensions in IBS patients.\textsuperscript{86,89} At least in the lower gut, these data may indicate that 5-HT\textsubscript{3} receptor antagonists reduce gut perception by modulating the visceroelastic properties of the gut wall.\textsuperscript{15} There is indeed evidence that alosetron increases the compliance in the colon.\textsuperscript{33,86} However, the effects of both alosetron and ondansetron on rectal compliance have been less conclusive.\textsuperscript{82,84,87} Furthermore, neither alosetron, ondansetron nor tropisetron have been shown to alter the visceroelastic properties of the stomach.\textsuperscript{82,85,88} Thus, tonic or visceroelastic
modulation (that may explain their proposed viscerosensory effects) does not seem
to represent a generalised feature of 5-HT₃ receptor antagonists throughout the
gastrointestinal tract.

Despite the lack of evidence supporting a direct viscerosensory effect inhumans, 5-HT₃ receptor antagonist may still alter the perception of gastrointestinal
sensations via indirect mechanisms. For example, gastric distension combined with
simultaneous intraduodenal infusion of lipids induces nausea in healthy volunteers,
which is reduced by ondansetron.⁹⁰ Similarly, alosetron partly reduced the increased
perceptual response to colonic distension that is associated with intraduodenal
infusion of lipids in IBS patients.⁹¹ These lipid-induced sensory changes involve
neurohumoral changes such as the release of cholecystokinin,³²,³³ but have also
been proposed to involve the central and/or autonomic nervous system.³³ Using a
PET study in patients with IBS, it was shown that alosetron altered the cerebral
responses to rectosigmoid distension in specific brain regions corresponding with
centres that are known to be involved in the autonomic and emotional
responsiveness to visceral stimuli.⁹¹ In addition, there was no evidence for
decreased afferent input to brain regions that encode the intensity of pain, which is
expected if alosetron would have a direct inhibitory effect on peripheral afferent
signalling. Thus, together with the evidence that 5-HT₃ receptors can be
demonstrated at multiple sites within the brain and brain stem,²⁹,³³ the clinically
observed effects of 5-HT₃ receptor antagonists on symptom perception may, at
least in part, be centrally mediated. These central effects may involve the
pharmacological modulation of circuits regulating autonomic functioning and/or
the emotional-affective processing of perceived gut stimuli.

Clinical efficacy: 5-HT₃ antagonists have been under attention primarily for the
treatment of IBS. Two large, multinational, dose-ranging, placebo controlled trials
evaluating the efficacy of alosetron in IBS patients revealed that the drug was
effective, but only in female patients.⁹⁴,⁹⁵ The first study evaluated 302 patients, of
whom 202 were female.⁹⁴ Based on the primary efficacy endpoint (adequate relief of
pain and discomfort at least 6 of the 12 weeks’ trial duration), the maximal
therapeutic gain of alosetron over placebo was 27% in female patients receiving the
lowest dose (1 mg twice daily). In the second study, a total of 462 patients were
included (335 female).⁹⁵ Relative to placebo, alosetron induced a maximum
difference of 12% points on the proportion of pain free days (primary endpoint) in
females receiving the highest dose (2 mg twice daily). Apart from the different
endpoints, the differences in therapeutic gain between these studies may be
explained by the patient selection. Since alosetron has the potential of slowing
down gut transit and enhancing absorption,⁶⁶ the first study excluded constipation
predominant IBS patients, whereas the second study only excluded patients with
severe constipation (i.e. one or less bowel movements per week). Indeed in both
studies, alosetron significantly increased stool consistency and decreased defecation
frequency, with the most common reported adverse effect being constipation. The
consistent finding that male patients did not report significant improvements in
pain and discomfort scores may be related to gender differences in the response to
alosetron. However, it should be emphasised that the lack of demonstrable effect may at least be partly explained by the relative low number of male patients participating in both studies (33% and 27%, respectively), since the sample sizes were calculated based on the total number of subjects (i.e. male and female).

Based on the experience from these earlier studies, the efficacy and tolerability of alosetron was further evaluated in female, diarrhoea predominant IBS patients only. Indeed, three large, high quality trials showed that alosetron (1 mg twice daily) was effective in relieving pain/discomfort or urgency in women with diarrhoea predominant IBS (Figure 4). The therapeutic gain relative to placebo for these respective primary efficacy endpoints was 12%, 17% and 16% respectively, with placebo responses ranging from 26% to 57%. In addition, alosetron significantly improved overall symptom ratings and improved bowel habits by increasing stool consistency and decreasing defecation frequency. The most frequent side effect was constipation (range: 22% to 39%), being mostly mild to moderate in severity. These results lead to the approval of alosetron by the Food and Drug Administration (FDA) as a treatment for a distinct subgroup of patients with IBS (i.e. female, diarrhoea predominant). However, the compound was soon withdrawn from the market by the manufacturer because of serious adverse effects (worldwide 51 cases of ischaemic colitis including 5 fatalities and 21 cases of severe, partly complicated constipation by the end of 2000). Alosetron is now again under evaluation in the US under restrictive guidelines.

**Figure 4.** Clinical efficacy of the 5-HT₃ antagonist alosetron in patients with IBS: Proportion of patients with adequate relief of pain and discomfort per week with alosetron 1 mg twice daily (n = 324) and placebo (n = 323). * P< 0.05 versus placebo. Adapted from with permission (Elsevier).
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Preliminary reports suggest that cilansetron, another 5-HT3 antagonist, may also be effective for the treatment of non-constipated IBS patients. In a dose ranging, placebo controlled study including 454 patients, cilansetron (1 mg and 8 mg) induced a 22% point increase for the response rate on the primary efficacy endpoint (i.e., adequate relief). Similar to alosetron, cilansetron also improved secondary parameters such as stool consistency, defecation frequency and abdominal pain. However in contrast, the benefits were seen not only in female but also in male patients, an issue that may require further study. Cilansetron is currently under evaluation in phase III trials.

In addition to IBS, the efficacy of alosetron has also been evaluated in FD, in a single large, placebo controlled, dose-ranging study (0.5 mg, 1.0 and 2.0 mg twice daily), involving 320 patients of whom 220 (69%) were female. Overall, the 1.0 mg dose induced favourable rates for adequate relief (primary endpoint) compared to placebo, the therapeutic gain being 11%. If female patients were analysed separately, responder rates increased to a 13% point difference with placebo. Similar to IBS, no detectable differences were observed in males, again representing a minority of the participants. In addition to global relief, alosetron decreased the percentage of days with dyspeptic symptoms of early satiety and postprandial fullness during the 12-week treatment period, but not the severity scores of individual dyspeptic symptoms.

5-HT4 agonists

Viscerosensory effects in humans: The combined 5-HT3/5-HT4 receptor agonist cisapride (10 mg four times daily), decreased rather than increased the perception and discomfort thresholds during both isobaric and isovolumetric gastric distensions. This effect was associated with a significant reduction in gastric wall tone and increased compliance. Others reported no effects of cisapride on the mechanical and sensory responses to isobaric gastric distensions. In a preliminary report, the more specific 5-HT4 receptor partial agonist tegaserod decreased gastric wall tone and tended to increase gastric compliance, without altering the perceptual responses to distension.

In the lower gut, tegaserod (6 mg twice daily for 8 days) did not significantly alter the intensity of sensations induced by both slow ramp volume distensions and phasic pressure distensions. Despite this, tegaserod significantly reduced the inhibitory effects on the RIII reflex elicited by rectal distensions, suggesting that the drug may somehow interact with the spinal processing of visceral sensory information. The authors further suggested that these sensory effects are probably limited to a distinct functional sub population of mechanoreceptors, since the inhibiting effects on the RIII reflex were only observed during slow ramp distensions and not during rapid phasic distensions.

Clinical efficacy: Cisapride has been available primarily as a prokinetic in the treatment of FD, until its potential of inducing cardiac dysrhythmias led to its...
withdrawal. The drug is now only available under narrowly defined restrictions.\textsuperscript{106} Nevertheless, several randomised, placebo controlled studies have shown the potential benefit of cisapride (4-10 mg three times daily) for relieving symptoms in FD. The results of these studies (13 in total) have been best summarised by two meta-analyses.\textsuperscript{107,108} The first analysis pooled the results of studies that defined response by the global assessment of treatment effect.\textsuperscript{107} This could reflect assessments made by the investigators and/or the patients involved in the studies. If the response was defined as excellent or good, cisapride offered clear benefit over placebo (odds ratio 3.38; 95\% CI: 2.04-5.58). In addition, studies that assessed these symptoms reported significant benefit for cisapride over placebo for epigastric pain, early satiety, bloating and nausea. The second analysis pooled the results of those studies with 'clear clinical criteria of treatment success', excluding severity scores and intensity of single symptoms.\textsuperscript{108} Here, the probability of treatment success compared to placebo was 0.34 (95\% CI: 0.21-0.46). Thus, both meta-analyses found a significant overall therapeutic gain for cisapride over placebo in patients with FD.

In IBS, as opposed to 5-HT\textsubscript{3} antagonists, the newly developed 5-HT\textsubscript{4} agonists seem promising for the treatment of patients with a constipation predominant bowel habit, because of their ability to stimulate peristalsis and chloride secretion within the gut.\textsuperscript{66} Three large published, double blind, randomised, placebo controlled trials, have evaluated the effect of tegaserod (a partial 5-HT\textsubscript{4} agonist) in patients with constipation predominant IBS.\textsuperscript{109-111} In each trial, global relief of IBS symptoms, obtained during a 12-week treatment period, was defined as the primary efficacy measure. The first trial was a dose ranging study with 2 and 6 mg tegaserod twice daily, including 881 IBS patients of whom 731 (83\%) were female. Overall, responder rates for global relief at end point were 35\%, 47\% and 46\% for patients receiving placebo, 2 and 6 mg, respectively. Differences were statistical significant for both doses. In the 6 mg dose, tegaserod also significantly reduced weekly abdominal pain scores compared with placebo. However, the relative reduction from baseline in daily abdominal pain/discomfort was modest: approximately 24\% and 18\% at endpoint for tegaserod and placebo, respectively.

The second trial involved 1519 female IBS patients, randomised to receive 6 mg tegaserod or placebo twice daily.\textsuperscript{110} Responder rates for global relief were significantly higher in the tegaserod group than in the placebo group (44\% and 39\%, respectively; see Figure 5). Differences between tegaserod and placebo in the changes from baseline at endpoint for abdominal pain/discomfort again were small, albeit statistically significant: 1.0 for tegaserod versus 0.8 for placebo on a seven-point ordinal scale.

The most recent trial with tegaserod (6 mg or placebo twice daily) included 520 IBS patients from the Asia-Pacific region (88\% female).\textsuperscript{111} After 12 weeks, 62\% reported satisfactory relief of IBS symptoms with tegaserod and 44\% with placebo. Compared to baseline, tegaserod and placebo reduced the number of days with at least moderate abdominal pain/discomfort from 15.5 to 8.1 and from 15.2 to 9.5 days per 28 days, respectively, the differences being statistically significant.
Figure 5. Clinical efficacy of the 5-HT₄ agonist tegaserod in patients with IBS: Weekly proportion of patients who were completely, considerably or somewhat relieved with tegaserod 6 mg twice daily (n = 767) and placebo (n = 752). * P < 0.05 versus placebo. Adapted from [10] with permission (Blackwell publishing).

In general, tegaserod consistently and significantly improved bowel habits by increasing defecation frequency and decreasing stool consistency. The overall effects were observed within the first week and persisted throughout the trial period. After withdrawal of the study medication (two studies included a washout period) [10,11] responder rates declined rapidly. The most frequently observed adverse effect was diarrhoea (ranging from 2.3% to 9.6% across these studies). During its clinical evaluation so far, no serious adverse events have been reported and the drug was approved by the FDA in July 2002 for females with constipation predominant IBS [10,10]

The preliminary results of a dose ranging, phase II multicentre study in 271 patients with FD showed only trends towards better satisfactory relief (primary efficacy measure) with 12 mg tegaserod versus placebo, the responder rates being 55% and 43% respectively (NS) [12]. Tegaserod also showed some benefit over placebo in reducing individual dyspeptic symptoms of early satiety and postprandial over the eight-week intervention period.

Prucalopride (a full 5-HT₄ agonist) has not been tested in patients with IBS. However the compound accelerates bowel transit in patients with functional constipation, a condition with significant symptom overlap with constipation predominant IBS [113]. Unfortunately, prucalopride is now not longer under evaluation.

Serotonergic agents: Summary

Taken together, these data suggest that serotonergic agents interact act several levels and may result in symptomatic improvement via their regulatory effect on motility, enteric reflexes, secretion and absorption. The observed effects on
symptom perception probably represent a subtle interaction between these factors, rather than a direct effect on visceral sensitivity.

The clinical benefits of 5-HT₄ agonists and 5-HT₃ antagonists for patients with FIGDs, in particular IBS, have been well studied in several high quality trials. Given their potential of modulating a variety of bowel functions via their action on 5-HT receptors, these newer drug classes have been introduced with high expectations regarding their possible role in the management of FIGDs. However, the available evidence for their clinical efficacy may be somewhat disappointing. In IBS, the percentage point difference with placebo for global symptom improvement maximally reached an acceptable 27% for alosetron but was generally lower (range: 12-27 %), whereas tegaserod reached a maximal therapeutic gain of 18% (range: 5-18 %). In FD, alosetron and cisapride induced a therapeutic gain over placebo of 13% and 34%, respectively, based on global symptom assessment. It should be emphasised that placebo responses in FIGD patients are generally high, partly due to the high rate of symptom fluctuation and their self-limiting nature. Indeed, in the above-mentioned studies, responder rates during placebo ranged between 26% and 57%, partly explaining the relative minor improvements of the active drug relative to placebo (Figures 4 and 5). This also explains that, despite a priori patient selection based on bowel habit and gender, very large trials were needed to provide statistically significant differences with placebo. Notwithstanding the relatively small additional efficacy, 5-HT receptor agonists and antagonists will certainly find their way to routine clinical practice.

**ANTIDEPRESSANTS**

**General**

Antidepressants have been widely used in the treatment of FIGDs, mainly because FIGD patients show high levels of comorbid depression and anxiety. However, in addition to their psychotropic action, antidepressants have neuromodulatory and analgesic properties, of which the most convincing clinical evidence comes from experimental models of somatic pain and various somatic pain syndromes. These studies have demonstrated the analgesic potency of both tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), although TCAs, in particular amitriptyline, seem superior in this perspective and are certainly the best studied. The mechanisms by which antidepressants have analgesic effects are largely unknown, but may involve serotonergic, noradrenergic and opioidergic systems. This may include modulation of perceptive and/or integrative responses to painful stimuli in the brain or activation of descending, inhibitory pathways. The possible involvement of spinal and/or peripheral mechanisms has not been well established. Based on these findings, antidepressants have been proposed to reduce visceral sensitivity, and there are several studies in humans available addressing this issue.
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**Tricyclic antidepressants (TCAs)**

*Viscerosensory effects in humans:* The effects of TCAs on visceral sensitivity have been unequivocal. For example in healthy volunteers, pre-treatment with imipramine (ascending dose of 25 to 75 mg over 12 days) increased the volume at which the threshold for pain was reached during oesophageal distension, without an effect on the pressure threshold for pain\(^{119}\). Three weeks pre-treatment with 50 mg amitriptyline, another TCA, had no effect on perceptual thresholds during phasic, isobaric distensions of both the oesophagus and the rectum.\(^{116}\) In addition, in FD patients, 50 mg amitriptyline for four weeks did not alter the perceptual responses to balloon distension of the stomach.\(^{120}\) In contrast, in a comparative study with group psychotherapy, amitriptyline, in an ascending dose of 10 to 25 mg/day for six weeks, increased the threshold for pain during phasic isobaric rectal distension in patients with IBS.\(^{121}\) In patients receiving group psychotherapy, the pain thresholds remained unaltered. Despite this control group, the interpretation of these results remain difficult, since there was no placebo group included in the study.

More recently, it was shown that pre-treatment with 50 mg amitriptyline for four weeks tended to reduce pain ratings upon rectal distension in IBS patients, but only under laboratory stress conditions (sound of babies crying during the procedure).\(^{122}\) During relaxing music, no difference with placebo were observed. Combined fMRI measurements showed that during painful distension and stress, amitriptyline reduced brain activation overall by 2.3 %, relative to the placebo condition. Greatest reductions were seen in brain regions involved in the midline affective pain system, such as the ACC and thalamus. In addition, reductions were seen in limbic, association and sensory cortices. These interesting data suggest that TCAs may modulate viscerosensory changes associated with mental stress, which could contribute to their clinical benefit in FIGDs.

*Clinical efficacy:* There is increasing evidence that TCAs are effective in the treatment of FIGDs. A recent meta-analysis of eleven published, randomised placebo controlled trials on the effectiveness of antidepressants in FIGDs (FD, IBS or both) showed a favourable outcome for both general symptom relief and pain scores during treatment with TCAs.\(^{123}\) For general symptom relief, the odds ratio overall was 4.2 (95 % CI: 2.3-7.9) in favour of TCAs over placebo. For pain, the standardised mean difference was 0.9 in favour of TCAs (95 % CI: 0.6-1.2). However, this analysis also revealed that the overall quality of the studies was low to moderate, mostly because of the limitations of blinding the study because of side effects. Another weakness was that all but two studies that were analysed failed to exclude patients with concomitant depression.\(^{123}\) More recently, a large, well-designed trial, comparing desipramine versus placebo in female patients with painful functional bowel disorders, further explored these issues.\(^{124}\) A total of 216 patients were randomised 2:1 to receive desipramine (in an ascending dose of 50 to 150 mg over three weeks) or placebo for a total period of 12 weeks. Of these patients, the majority was diagnosed as having IBS (79 %). Other diagnoses included functional constipation, chronic functional abdominal pain, and unspecified FIGD. According to the intention to treat analysis, the responder rate at endpoint (defined by a mean score over eight items evaluating patient
satisfaction) for desipramine was not significantly different compared with placebo (60 % and 47 %, respectively). In contrast, the per protocol analysis at endpoint showed significant higher response rates for the active treatment versus placebo (69 % versus 49 %). The differences in response rates further increased if patients with undetectable blood levels of desipramine were excluded from the analysis (73 % versus 49 %). Given the fact that 29 of the 51 dropouts (57 %) in the study occurred because of side effects, primarily involving patients receiving desipramine (26 patients versus placebo: 3), these data suggest that if the drug is tolerated and actually taken, antidepressant treatment is effective in FIGDs.124 Regarding the issue of concomitant depression, sub-analysis performed in patients with signs of depression (Beck Depression Inventory) versus no depression revealed that the latter had higher response rates. These data further support the concept that the beneficial effects of antidepressants may be independent from their psychotropic action.125

In FD, efficacy studies with TCAs are lacking. However, a small placebo controlled, crossover study with amitriptyline (50 mg daily for four weeks) including seven patients with FD reported a significant reduction in subjective symptoms. Clearly, these data need to be confirmed further.

**Selective serotonin reuptake inhibitors (SSRIs)**

Viscerosensory effects in humans: The SSRI paroxetine (20 mg/day for seven days) did not alter the thresholds for perception or discomfort during isobaric gastric distension in healthy volunteers.126 In addition, no effects on gastric compliance were observed. In contrast, venlafaxine (150 mg), a SSRI and norepinephrine reuptake inhibitor, increased colonic compliance and tone in healthy volunteers, without affecting the sensitivity to isobaric colonic distension.77

Similar to TCAs, little is known about the effects of SSRIs on visceral sensitivity in FIGDs. The only data available are from one study in IBS, showing that fluoxetine (20 mg/day for six weeks) did not alter perceptual responses to phasic isobaric distension or volume ramp distension of the rectum.125 This lack of effect was seen in both normosensitive and hypersensitive patients, further questioning the direct viscerosensory effects of antidepressants in FIGDs.

**Clinical efficacy:** Despite their widespread clinical use, studies evaluating the efficacy of SSRIs in FIGDs have only recently become available. Paroxetine (20 mg/day for three months) improved health related quality of life in patients with IBS significantly better, compared with 'treatment as usual"127. The study included 86 patients in each group, plus 85 additional patients receiving psychotherapy. The improvements of intensity scores for abdominal pain (primary outcome measure) in each treatment did not significantly differ. However, paroxetine induced a significantly greater reduction in the number of pain free days compared with the 'treatment as usual' group (mean difference from baseline: -8.5 and -4.3 days/month, respectively).

A second study involved 40 non-depressed IBS patients, randomised to receive fluoxetine (20 mg/day) or placebo for six weeks. At endpoint, global symptom
relief was obtained in 53% of patients receiving fluoxetine versus 43% receiving placebo, which was not statistically different.\textsuperscript{125} Interestingly, compared to baseline, fluoxetine significantly reduced the proportion of patients reporting significant abdominal pain (from 89% to 53%), whereas no change was observed during placebo (from 76% to 76%). No significant effects were observed for individual gastrointestinal symptoms.

**Antidepressants: Summary**

There is increasing evidence that antidepressants are useful for the treatment of FIGDs, in particular for the treatment of pain. However, little is known about their mechanism(s) of action in these disorders, in particular, their proposed role in reducing visceral perception. Based on the data available in the literature, there is little or no evidence that antidepressants reduce visceral sensitivity in humans. Changes in symptom perception, in particular pain, may therefore reflect a modulatory action of antidepressants on the integrative processing of gut stimuli within the brain. Studies using functional brain imaging techniques have only recently become available, but seem to support such a mechanism.\textsuperscript{122} Issues that need further exploration for the future application of antidepressants in FIGDs include the impact of possible concomitant psychiatric disease, comparison between different classes of antidepressants (e.g. TCAs, SSRIs, partial norepinephrine reuptake inhibitors) and possible differential effects for visceral hypersensitive and normosensitive patients.\textsuperscript{125}

**SOMATOSTATIN ANALOGUES**

**General**

Somatostatin (SST) and its synthetic analogue octreotide have been shown to be effective in the treatment of different clinical pain syndromes,\textsuperscript{128,129} and there is pre-clinical evidence that octreotide also possesses visceral analgesic effects.\textsuperscript{130} Of the five cloned SST receptors, octreotide has a high affinity for three subtypes (SST receptor 2, 3 and 5). SST and its receptors have been demonstrated in the CNS (brain, spinal cord),\textsuperscript{131-133} and in the peripheral nervous system (primary afferents, DRG).\textsuperscript{133,134} The sites and/or mechanisms of action involved in the possible (visceral) analgesic effects of octreotide remain unknown. Although it seems unlikely that peripherally administered octreotide crosses the blood-brain barrier in significant amounts,\textsuperscript{135} the analgesic effects of octreotide in somatic pain have been demonstrated after both intrathecal and subcutaneous injection.\textsuperscript{128,129,136} In rats, significant visceral analgesic effects were observed when octreotide was administered intrathecally, but not after intravenous administration.\textsuperscript{130} In addition, no effects were seen on pelvic nerve afferent fibre responses to colorectal distension, suggesting that octreotide does not act peripherally.\textsuperscript{130} Therefore, it has been suggested that the analgesic effects of peripherally administered octreotide could result from activation of central sites unprotected by the blood-brain barrier, or from indirect central effects through the activation of vagal afferents.\textsuperscript{137}
However, the involvement of SST receptors on alternative peripheral afferent pathways not evaluated so far, can not be excluded.

Octreotide

Viscerosensory effects in humans: The viscerosensory effects of octreotide in humans have only been studied after subcutaneous administration of the drug (single dose of either 100 μg or 1.25 μg/kg). In healthy volunteers, octreotide reduced the perception of physiological sensations (oesophagus, stomach). However, discomfort/pain thresholds (stomach, rectum) during isobaric distension were not significantly altered by octreotide. In contrast, pain threshold and maximum tolerated volumes during slow ramp volume distension of the rectum were significantly increased by octreotide. No effects on oesophageal and rectal wall compliance were observed, whereas gastric wall compliance decreased rather than increased. The differential sensory effects during different intensities and protocols of gut distension may suggest that octreotide reduces afferent signalling upon activation of a subset of visceral mechanoreceptors. A similar interpretation was brought forward in another paper addressing the viscerosensory effects of tegaserod (see paragraph 5.2). Upon electrical rectal stimulation, octreotide significantly reduced perception scores, which was associated with decreased cerebral and spinal evoked potentials, further suggesting that the SST analogue reduces visceral perception via spinal afferent pathways.

In IBS, octreotide (100 μg and 1.25 μg/kg respectively) not only significantly increased volume thresholds to rectal distension, but also the thresholds for discomfort and pain during phasic, isobaric distension of the colon. In both studies, thresholds increased up to values comparable with those observed in healthy volunteers with no active treatment. Octreotide increased rectal compliance in the first study, evaluating patients with diarrhoea predominant IBS, but not in the second study evaluating non selected IBS patients.

Clinical efficacy: Because of their viscerosensory effects and possibly, modulatory effects of the elastic properties of the gut, SST analogues may be beneficial for the treatment of FIGDs. In addition, SST analogues may be effective by inhibiting gut motility and secretion, and by promoting absorption of luminal contents. Although there are no randomised controlled trials available on the clinical benefits of SST analogues for FIGDs, there is documented anecdotal evidence suggesting that octreotide may indeed be effective in relieving IBS symptoms. In addition, in an open label prospective study, 17 patients with severe refractory functional epigastric pain were treated with subcutaneous octreotide. The starting dose was 50 μg twice daily and was either maintained or increased to 100 μg twice daily, depending on the symptomatic response. After one month, 15 patients reported progressive improvement of pain intensity scores (median score: from 7.9 to 1.9 on a 10-cm visual analogue scale). The symptomatic benefit was maintained at 3 months, and even up to 11 to 27 months in those patients available for follow-up, whereas withdrawal of the medication led to recurrence of symptoms within 2
to 3 days. Symptom improvement was associated with a median weight gain of 3.5 kg at 3 months.

**SST analogues: Summary**

Although there are no randomised controlled trials available confirming the potential clinical benefits, there is certainly evidence that octreotide reduces visceral sensitivity in humans. Interestingly, considering the pooled data from the studies performed in healthy volunteers and in IBS patients, there may also be evidence for a differential effect between IBS patients and healthy subjects. For example in healthy volunteers, octreotide consistently (oesophagus, stomach, rectum) increased the perceptual thresholds for physiological sensations, but not for discomfort or pain. In contrast, in IBS patients octreotide significantly increased thresholds for discomfort and pain during colonic and rectal distensions, even up to levels comparable with healthy volunteers with no active treatment. Therefore, octreotide may specifically act by normalising the hypersensitive response in patients with FIGDs. This may for example suggest that in hypersensitive states, octreotide sensitive afferent pathways may be up-regulated or recruited. Other factors, such as possible modulatory effects on gut wall compliance, may also be involved.

**α2-ADRENERGIC AGONISTS**

**General**

The adrenergic nervous system plays an important role in modulating nociceptive processing. α2-Adrenergic agonist binding sites have been demonstrated along nociceptive pathways in the spinal cord, brain stem and forebrain, and activation of spinal α2-adrenergic receptors has been shown to play a role in antinociception. This may involve modulation of spinal neurotransmission at the level of the dorsal horn and/or activation of descending, inhibitory pathways. Alternatively, activation of adrenergic receptors in supraspinal centres may alter autonomic or emotional responses to visceral stimuli.

Clonidine, a selective α2-adrenergic agonist, has been shown to produce postoperative analgesia in humans. In addition, intrathecally administered clonidine has been shown to suppress both somato-motor and somato-visceral reflexes to noxious thermal stimulation in the rat. On the other hand, the specific visceral sensory effects of clonidine have not been well established in experimental studies.

**Clonidine**

*Viscerosensory effects in humans:* In healthy volunteers, clonidine (0.0125, 0.025 and 0.1 mg) dose-dependently reduced pain perception during phasic isobaric gastric distension and increased gastric wall compliance. Similarly, a single oral dose of clonidine (0.3 mg) reduced the perception of pain evoked by phasic isobaric colonic distension. Notwithstanding the observation that clonidine increased colonic compliance, the fact that clonidine reduces the perception of noxious stimuli, but
not of non-noxious, physiological sensations such as the perception of gas, may suggest that the drug acts as a true visceral analgesic.\textsuperscript{151} However, these finding were only partly confirmed by a consecutive, dose ranging study (placebo, 0.1, 0.2 and 0.3 mg).\textsuperscript{148} In this particular study, pain scores during isobaric colonic distension were only reduced by the 0.3 mg dose, whereas the sensation of gas was decreased significantly by all three doses of clonidine. In addition, the dose-responsiveness to clonidine on the sensation scores for gas paralleled the dose-related increase in colonic compliance. Thus, these data suggest that the reduction in colorectal tone may at least have influenced the perception of visceral sensations.

At present, there are no studies available regarding the effects of $\alpha_2$-adrenergic agonists such as clonidine on visceral sensitivity in FIGD patients. These studies are certainly required to confirm their proposed mechanism of action in the treatment of symptoms.

**Clinical efficacy:** So far, one randomised, placebo controlled exploratory trial with clonidine in IBS patients has been published.\textsuperscript{152} In this trial, 44 patients with diarrhoea predominant IBS received placebo, 0.05, 0.1 or 0.2 mg clonidine twice daily for four weeks. Clonidine 0.1 mg significantly improved stool consistency scores and the ease of stool passage, without objective changes in gastrointestinal transit. The magnitude of the mean differences with placebo for both secondary endpoints was approximately 0.8 points on a 0 to 7 nominal scale. Satisfactory relief (reported during at least 50% of the trial period) tended to be higher (0.1 mg: 67% versus placebo: 46%). The severity of side effects (mainly drowsiness, dizziness and dry mouth) was transient with the 0.1 mg dose, but was quite significant with the 0.2 mg dose, causing the two patients receiving 0.2 mg to drop out within the first three days.

**$\alpha_2$-Adrenergic agonists: Summary**

In healthy volunteers, clonidine consistently increased gastric and rectal compliance and reduced sensation scores during phasic isobaric distensions. Several arguments have been brought forward to illustrate the true viscerosensory effects of clonidine, as opposed to its indirect effects by increasing gut wall compliance. Clearly, the observed effects on gut tone and compliance certainly deserve consideration when interpreting the viscerosensory effects of clonidine in future studies. The available evidence may suggest some clinical benefit, however the adverse effects seem substantial if not intolerable, especially in the dose range needed to induce visceral analgesia in healthy volunteers (i.e. 0.3 mg). Further studies are needed to confirm the clinical potential of clonidine in patients with FIGD.
Chapter 1

SUMMARY AND DISCUSSION

Visceral hypersensitivity is a common feature in FIGDs and is generally regarded as an important factor in the pathogenesis and symptom generation of these disorders. Although sensory abnormalities can be demonstrated in up to 94%, depending on the definitions that are applied,\textsuperscript{5,22} visceral hypersensitivity has been a consistent finding in about one-half to two-thirds of patients presenting with either IBS or FD.\textsuperscript{153} Since the pathogenesis of FIGDs is multifactorial, hypersensitive patients may represent a different subgroup compared with normosensitive FIGD patients with regard to the generation of symptoms and their treatment. In particular, restoring normal sensitivity could be an attractive target for pharmacological interventions in these patients. This concept has attracted the interest of researchers from both the academia and pharmacological industry. Consequently, much progress has been made in the characterisation of the mechanisms and mediators modulating visceral sensitivity. In particular, several possible pharmacological targets have been identified to reduce visceral pain and to reverse the processes underlying the persistence of visceral hypersensitivity.\textsuperscript{2,16,21} So far, most of the available evidence comes from experimental animal models, whereas data from human studies are rather limited. In this review, we selected five drug classes that have been shown to exhibit visceral analgesic properties in experimental studies, and of which data were available regarding their clinical efficacy.

In contrast to animal studies, viscerosensory responses in humans largely depend on symptom assessment in response to visceral stimuli. These methods inevitably hold an element of subjectivity.\textsuperscript{27,29} The introduction of electrophysiological and imaging techniques may therefore be important to further expand our knowledge of the processes involved in visceral sensation.\textsuperscript{37} In addition, determination of the possible mechanisms of action of an investigational compound is difficult, because of methodological limitations. One of the difficulties in the interpretation of the true viscerosensory effects of a particular drug during mechanical distension of the gut relates to its viscoelastic properties.\textsuperscript{27,29} Changes in compliance or tone of the gut wall may alter volume thresholds, without associated effects on pressure-based distensions. In this perspective, one needs to distinguish drugs with pure visceral analgesic properties (such as the µ-opioid agonists fentanyl and κ-opioid agonist fedotozine) from those with mixed viscoelastic and viscerosensory effects (including the 5-HT\textsubscript{3} antagonists, 5-HT\textsubscript{1} and 5-HT\textsubscript{4} agonists, the α-adrenergic agonist clonidine and, possibly, the SST analogue octreotide).

At present, the focus of viscerosensory active drugs has been primarily on the treatment of IBS. In this view, much attention has been paid to the clinical benefits provided by the contemporary drug classes of 5-HT\textsubscript{4} agonists and 5-HT\textsubscript{3} antagonists.\textsuperscript{66} High quality trials revealed that their efficacy largely depends on bowel habit and gender. The 5-HT\textsubscript{4} agonist tegaserod has been registered as treatment for female, constipation predominant IBS patients, whereas alosetron is efficacious in female, diarrhoea predominant IBS patients.\textsuperscript{110} Although these
findings suggest that interference with gastrointestinal motility and/or secretion, rather than with visceral sensation determines efficacy, these studies do show that adequate patient selection is of crucial importance. So far, clinical trials evaluating the effect of visceral analgesics have only been performed in unselected populations of IBS patients. For example in the fedotozin study evaluating the visceroceptive effects in IBS, the investigators carefully excluded normosensitive patients.\textsuperscript{55} Unfortunately, no such selection was made for patients that underwent clinical evaluation of fedotozin.\textsuperscript{57,58} Clearly, this may have influenced the rather disappointing outcome of these studies. In addition, in the study on the SSRI antidepressant fluoxetine for IBS, post-hoc analysis revealed that fluoxetine reduced abdominal pain, but only in patients characterised by hypersensitivity to rectal distension.\textsuperscript{125} These data illustrate that future trials evaluating visceral analgesics for FIGDs may need to consider sub-grouping of patients based on the presence of hypersensitivity.

Ideally, to select those patients, tools less invasive and less elaborate than the barostat, which currently serves as the gold standard, should be available. In patients with FD, attempts have been made to select hypersensitive patients based on their symptom profile. However, despite statistical associations with symptoms of postprandial pain, belching and weight loss,\textsuperscript{7} this approach is not clinically useful.\textsuperscript{79} In IBS, comparable data are lacking, but in our laboratory no associations between symptoms and the presence of hypersensitivity to rectal distension could be demonstrated in a cohort of 92 IBS patients (unpublished results). Other methods of selecting FD subgroups with hypersensitivity include the nutrient- and water drink test, but again with disappointing sensitivity and specificity.\textsuperscript{79} Recent studies suggest that functional brain imaging may provide valuable insights in how certain drugs may modulate the visceroceptive processing at the level of the brain.\textsuperscript{20,91} These techniques may help to select patients for future studies addressing the possible differential clinical efficacy of visceral analgesics in hypersensitive versus normosensitive FIGD patients, but clearly, these tools are currently not available for routine clinical use. Therefore, to further explore the concept of visceral hypersensitivity in FIGDs, assessing gut sensitivity in the future will continue to require barostat measurements.

In conclusion, based on the current clinical evidence, the concept of targeting visceral hypersensitivity as a treatment for of FIGDs is still controversial. In order to proof this concept, we propose that patient selection should be based on the presence of visceral hypersensitivity when evaluating compounds that exhibit 'true' visceroceptive effects.

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